The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

adjuvant

SYLLABICATION: ad ju vant

PRONUNCIATION: ăj'ə-vənt

NOUN: 1. A pharmacological agent added to a drug to increase or aid its effect.
2. An immunological agent that increases the antigenic response.

ETYMOLOGY: From Latin *adiuvāns*, *adiuvant-*, present participle of *adiuvāre*, to help. See aid.

part of the toxicological evaluation, PDAPP mouse brain pathology was extensively examined as part of the efficacy endpoints. No sign of treatment related adverse effect on brain morphology was noted in any of the studies. These results indicate that AN1792 treatment is well tolerated and at least substantially free of side effects.

XI. Therapeutic Treatment with Anti-Aβ antibodies

This examples tests the capacity of various monoclonal and polyclonal antibodies to Aβ to inhibit accumulation of Aβ in the brain of heterozygotic transgenic mice.

1. Study Design

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to Aβ. Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine Aβ-specific monoclonal antibodies, 2H3 (directed to Aβ residues 1-12), 10D5 (directed to Aβ residues 1-16), 266 (directed to Aβ residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to Aβ residues 33-42). A fifth group was treated with an Aβ-specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

The monoclonal antibodies were injected at a dose of about 10 mg/kg (assuming that the mice weighed 50 g). Injections were administered intraperitoneally every seven days on average to maintain anti-Aβ titers above 1000. Although lower titers were measured for mAb 266 since it does not bind well to the aggregated AN1792 used as the capture antigen in the assay, the same dosing schedule was maintained for this group. The group receiving monoclonal antibody 2H3 was discontinued within the first three weeks since the antibody was cleared too rapidly in vivo. Animals were bled prior to each dosing for the measurement of antibody titers. Treatment was continued over a six-month period for a total of 196 days. Animals were euthanized one week after the final dose.

Table 10

EXPERIMENTAL DESIGN OF STUDY 006

Treatment Group	N[a]	Treatment Antibody	Antibody Specificity	Antibody Isotype
1	9	none (PBS alone)	NA[b]	NA
2	10	Polyclonal	Aβ1-42	mixed
3	0	mAb[c] 2H3	Aβ1-12	IgG1
4	8	mAb 10D5	Aβ1-16	IgG1
5	6	mAb 266	Aβ13-28	IgG1
6	8	mAb 21F12	Aβ33-42	IgG2a

Footnotes

a. Number of mice in group at termination of the experiment. All groups started with 10 animals per group.
b. NA: not applicable
c. mAb: monoclonal antibody

2. Materials and Methods

a. Preparation of the Antibodies

The anti-Aβ polyclonal antibody was prepared from blood collected from two groups of animals. The first group consisted of 100 female Swiss Webster mice, 6 to 8 weeks of age. They were immunized on days 0, 15, and 29 with 100 μg of AN1792 combined with CFA/IFA. A fourth injection was given on day 36 with one-half the dose of AN1792. Animals were exsanguinated upon sacrifice at day 42, serum was prepared and the sera were pooled to create a total of 64 ml. The second group consisted of 24 female mice isogenic with the PDAPP mice but nontransgenic for the human APP gene, 6 to 9 weeks of age. They were immunized on days 0, 14, 28 and 56 with 100 μg of AN1792 combined with CFA/IFA. These animals were also exsanguinated upon sacrifice at day 63, serum was prepared and pooled for a total of 14 ml. The two lots of sera were pooled. The antibody fraction was purified using two sequential rounds of precipitation with 50% saturated ammonium sulfate. The final precipitate was dialyzed against PBS and tested for endotoxin. The level of endotoxin was less than 1 EU/mg.

The anti-Aβ monoclonal antibodies were prepared from ascities fluid. The fluid was first delipidated by the addition of concentrated sodium dextran sulfate to ice-cold

for the measurement of antibody titers. Treatment was continued over a six-month period for a total of 196 days. Animals were euthanized one week after the final dose.

Table 12

Experimental Design of Study 006

Treatment Group	N[a]	Treatment Antibody	Antibody Specificity	Antibody Isotype
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Footnotes
a. Number of mice in group at termination of the experiment. All groups started with 10 animals per group.
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Literature Search Strategy and the Databases Searched

A comprehensive computer data base search was conducted of both the patent and scientific literature in an attempt to identify any disclosures of the use of thimerosal as an adjuvant. The search strategy was to look for (a) "thimerosal" or its synonyms as listed in the Chemical Abstracts Registry File (merthiolate, mercurothiolate, mersonin, thimersalate, etc.), in combination with (b) "adjuvant" or "vaccine". This strategy was designed to identify disclosures of thimerosal as an adjuvant, or as a component of a vaccine formulation for any purpose.

The databases searched included Dialog and Questel Orbit, as well as Chemical Abstracts, V ETU, VETB and Russian Science on STN. Specific Dialog databases searched included Derwent World Patents Index (WPI), JAPIO, Chinese Patents Abstracts, International Pharmaceutical Abstracts, EMBASE, BIOSIS, CAB Abstracts, MEDLINE, AGRICOLA, Life Sciences Collection, AGRIS, Pascal, World Translations Index, Dissertation Abstracts, Inside Conferences, Conference Papers Index, JICST, Current Contents Search, and Derwent Drug File. Specific Questel Orbit databases searched included EPAT, PCTPAT, Pharm and Pluspat (Comprehensive WorldWide Patents).

"Thimerosal in Vaccines"

"Thimerosal in Vaccines" from the website of the Center for Biologics Evaluation and Research (CBER), identifies thimerosal as a preservative, not an adjuvant, used in a number of biological and drug products, including many vaccines. Further "Thimerosal in Vaccines" states that thimerosal is one of the most widely used preservatives in vaccines." The CBER is part of the U.S. Food and Drug Administration, and is responsible for the review and approval of vaccines for human use. The CBER website address is (www.fda.gov/cber/vaccine/thimerosal.htm).

Pertinent portions of this printout include the following:

"Thimerosal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes. Over the past several years, because of an increasing awareness of the theoretical potential for neurotoxicity of even low levels of organomercurials and because of the increased number of thimerosal containing vaccines that have been added to the infant immunization schedule, concerns about the use of thimerosal in vaccines and other products have been raised. Indeed, because of these concerns, the Food and Drug Administration has worked with, and continues to work with, vaccine manufacturers to reduce or eliminate thimerosal from vaccines." (*See* p. 1.)

"To begin, we need to answer two questions-what are preservatives and why are they used in vaccines. For our purposes, preservatives may be defined as compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi. They are used in vaccines to prevent microbial growth in the event that the vaccine is accidentally contaminated, as might occur with repeated puncture of multi-dose vials. In some cases, preservatives are added during

manufacture to prevent microbial growth; with changes in manufacturing technology, however, the need to add preservatives during the manufacturing process has decreased markedly." (*See* p. 1.)

"Thimerosal, which is approximately 50% mercury by weight, has been one of the most widely used preservatives in vaccines." (*See* p. 3.)

Derwent File 351: Derwent WPI Database Abstract for U.S. Patent No. 5,989,566
and
U.S. Patent No. 5,989,566

The Derwent File 351: Derwent WPI database abstract for U.S. Patent Number 5,989,566 was in error in stating that the patent disclosed the use of thimerosal as an adjuvant. The abstract of U.S. Patent 5,989,566, stated at the end of the second paragraph: "The adjuvant is e.g. thimerosal, formaldehyde, phenol, propylene glycol, etc." A review of the actual text of the patent reveals that the abstract is in error. Thimerosal is mentioned, but only as a preservative, in the text of U.S. Patent 5,989,566 as follows.

Column 5, line 66-column 6, line 5: "In a preferred process of the present invention, a preservative is added to the second suspension prior to step (d). Preservatives suitable for use in the present invention include thimerosal ([(o-carboxyphenyl)-thio]ethylmercury sodium salt), formaldehyde, phenol, propylene glycol, glycerol, esters of p-hydroxybenzoic acid, benzoic acid and sodium benzoate with thimerosal being preferred." (Emphasis supplied.)

* * *

Column 7, lines 17-27: "The moxidectin/6 in 1 vaccine composition identified as composition number 1 in Table I is prepared by ... adding a 1.3% wt/wt thimerosal solution (7.7 mL) ...." (Emphasis supplied.)

* * *

Derwent File 351: Derwent WPI Database Abstract for U.S. Patent No. 5,989,566
and
U.S. Patent No. 5,989,566

Claim 14:

"14. The vaccine composition according to claim 1 wherein the preservative is selected from the group consisting of thimerosal, formaldehyde, phenol, propylene glycol, glycerol, esters of p-hydroxybenzoic acid, benzoic acid and sodium benzoate. (Emphasis supplied.)

* * *

Claim 15:

"15. The vaccine composition according to claim 14 wherein the preservative is thimerosal." (Emphasis supplied.)

Furthermore, the only references to "adjuvant" in the patent list conventional adjuvants – not thimerosal, as shown by the abstract, the specification at column 1, lines 59-65, column 2, lines 14-18 and 26-35, column 5, lines 13-37 and 54-59, column 6, lines 10-35, and claims 1, 3, 10, 11 and 17. Claim 1 is exemplary:

"1. A vaccine composition consisting essentially on a weight to volume basis about 0.05% to 2.5% of a macrolide compound or mixtures of macrolide compounds; about 0.1% to 6% of a water-soluble organic solvent; about 1% to 8% of a dispersing agent; about 10% to 50% of an adjuvant; at least one antigen; up to about 0.1% of a preservative; and saline or water or a mixture thereof." (Emphasis supplied.)

Thus, it is clear that the database abstract for U.S. Patent Number 5,989,566 was in error in stating that the patent disclosed the use of thimerosal as an adjuvant.

Chemical Abstracts Database Abstract for the Report Entitled,
"Injection of Newborn Mice with Seven Chemical Adjuvant
to Help Determine Their Safety in Use in Biologicals"
and
the Report Itself

The Chemical Abstracts database abstract for the report entitled, "Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety in Use in Biologicals" and the report itself do not disclose the use of thimerosal as an adjuvant. The abstract appeared in the Chemical Abstracts database in 1971. Although the report itself is dated June 19, 1969, Applicant does not know the exact date that "Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety in Use in Biologicals" was accessible to the public.

The Chemical Abstracts database abstract states in its entirety:

"Mice less than 24 hr old were injected s.c. with benzethonium chloride, ethylene chlorohydrin, ethylene glycol, methylparaben, phenol red, thimerosal, or pyridine. The mice were examd. after 15 months for evidence of carcinogenic activity. None of the compds. appeared to have oncogenic potential."

The sole focus of the report itself is the possible carcinogenic effects of thimerosal and six other chemicals in newborn mice. The only reference to thimerosal as an adjuvant is in the title of the report. There is no bibliography, so it is unclear why the word adjuvant is even referred to in the title.

Initially, it is noted that nothing in the body of the abstract or the report indicates that any of the seven compounds listed had immune modulating activity, or any other activity characteristic of an adjuvant. Indeed, the word "adjuvant" does not even appear in the body of the abstract or the report. Applicants respectfully submit that the use of the word "adjuvant" in

Chemical Abstracts Database Abstract for the Report Entitled,
"Injection of Newborn Mice with Seven Chemical Adjuvants
to Help Determine Their Safety in Use in Biologicals"
and
the Report Itself

the title is inappropriate. None of the other six compounds tested is accepted for use as an adjuvant by persons of ordinary skill in the art. Phenol red is a dye indicator, ethylene glycol is an ingredient in anti-freeze, and benzethonium chloride and methylparaben are preservatives. Several of the compounds are totally unsuitable for administration to humans. For example, pyridine, is known to be toxic to the liver. Ethylene glycol and ethylene chlorohydrin are also toxic.

Because thimerosal is grouped with the other six compounds which are not adjuvants, and thimerosal is not distinguished from those compounds, a person of ordinary skill in the art reading the abstract or the report would not conclude that thimerosal may be used as an adjuvant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Dale B. Schenk

Application No.: 09/724,953

Filed: November 28, 2000

For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE

Examiner: Christopher J. Nichols

Art Unit: 1647

DECLARATION UNDER 37 C.F.R. § 1.132 OF MARTIN KOLLER, M.D., M.P.H.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Martin Koller, M.D., M.P.H., state as follows.

(1) My current position is Vice President, Clinical Development – North America at Elan Pharmaceuticals, the parent company of Neuralab, Inc, which is the assignee of the above-captioned application. I have designed and conducted many clinical trials and have experience at interpreting the results of clinical trials. A copy of my curriculum vitae is attached.

(2) A phase I human clinical trial (Study AN1792(QS-21)-102, henceforth designated as Study 102), was conducted in which AN1792 (42 amino acid synthetic formulation of Aβ) plus the adjuvant QS-21 was administered to patients suffering from Alzheimer's disease (AD) in comparison to a placebo control group (adjuvant alone). Study 102 was an exploratory, randomized, multi-center, double-blind, multi-dose, dose-escalation, adjuvant-controlled, safety, tolerability and immunogenicity study in patients with mild to moderate AD in which up to 8 injections of study drug were administered to patients over 18 months. The study was designed to assess 4 dose groups of AN1792(QS-21) with 20 patients per group, randomized to active vs placebo in a 4 to 1 ratio resulting in a total of 64 active and 16 control patients within the study.

(3) The functional disability of patients in this trial was assessed before treatment with Aβ (baseline) and at intervals thereafter. The clinical outcome measure used to measure functional disability was the Disability Assessment for Dementia (DAD) scale. The

DAD scale is an instrument developed and validated to measure the functional disability of patients with AD (Gelinas et al., Am. J. Occup. Ther. 53, 471-481 (1999)). Caregivers answered questions about the patients' ability to perform independently both instrumental and basic activities of daily living that had been attempted in the preceding two weeks. The proportion of DAD activities successfully completed out of those attempted was then calculated and reported as a percentage.

(4) The results from patients administered placebo versus patients administered Aβ are displayed in Figure 1 and listed in Table 1. The patients treated with Aβ were classified based on antibody titer ("Responders", "Sub-Threshold" titers, and "No Antibody" titers). The "Responders" were patients who had a titer that was 1:1,000 or greater 4 weeks after any injection or a titer that was 1:5,000 or greater at any time point after baseline. The "Sub-Threshold" titer responders are patients who had titers between 101-999 four weeks after any injection. The "No Antibody" titer patients are patients who had a titer that was 1:100 (the functional limit of the assay) four weeks after any injection.

(5) The average DAD score for all patients administered active versus placebo are listed in Table 1. A decline in score over time indicates a decline in functional abilities of the patients. The significant differences in the reduction of the decline noted in the treated patients as compared with the placebo patients is an indication that the treatment resulted in a beneficial effect by preserving functional abilities (e.g., the placebo group decline was greater than the decline seen the treated patients).

(6) The magnitude of the observed DAD effect in individual patients did not correlate strongly with the different magnitudes of antibody titer in the treated groups.

(7) An additional, exploratory phase IIa clinical trial (Study AN1792(QS-21)-201, henceforth Study 201) has been conducted in which AN1792(QS-21) was administered to human patients in comparison to placebo (normal saline). Study 201 was a multi-center, randomized, double-blind, multi-dose, placebo-controlled, safety, tolerability, and pilot efficacy study in patients with mild to moderate AD wherein 2 dose groups were studied (AN1792(QS-21) versus placebo with planned dosing of up to 6 injections to be administered over 12 months). The trial was halted after the vast majority of patients in the trial received only 2 doses of study

drug due to reports of encephalitis in a small number of patients (as has been reported in the press and scientific literature). Although study drug administration was halted, patients were followed for up to 12 months, and change from baseline to Month 12 DAD scores were still calculated. In this truncated trial, differences between the treated patients versus the placebo group did not reach statistical significance. Since dosing and the observation period for Study 201 had to be terminated early due to the occurrence of encephalitis, the DAD results from these two trials (Studies 102 and 201) are not comparable. In Study 201, patients were given fewer doses of study drug and the DAD scores were assessed over a shorter time period than in Study 102. Even with the greater number of dosages administered in Study 102, the change from baseline to Week 64 DAD scores failed to reach statistical significance (significance was defined as p-value < 0.05). The DAD data for studies 102 and 201 are summarized in Figure 2.

(8) In my opinion, the results from Study 102 described above provide evidence that administration of AN1792(QS-21) is of benefit in treating patients with Alzheimer's disease.

(9) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Martin Koller, M.D., M.P.H.

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JOL:rlc
PA 3307469 v1

Figure No. 1: Study AN1792(QS-21)-102

Mean DAD Adjusted Change from Baseline Scores (in percents)

by Titer Response

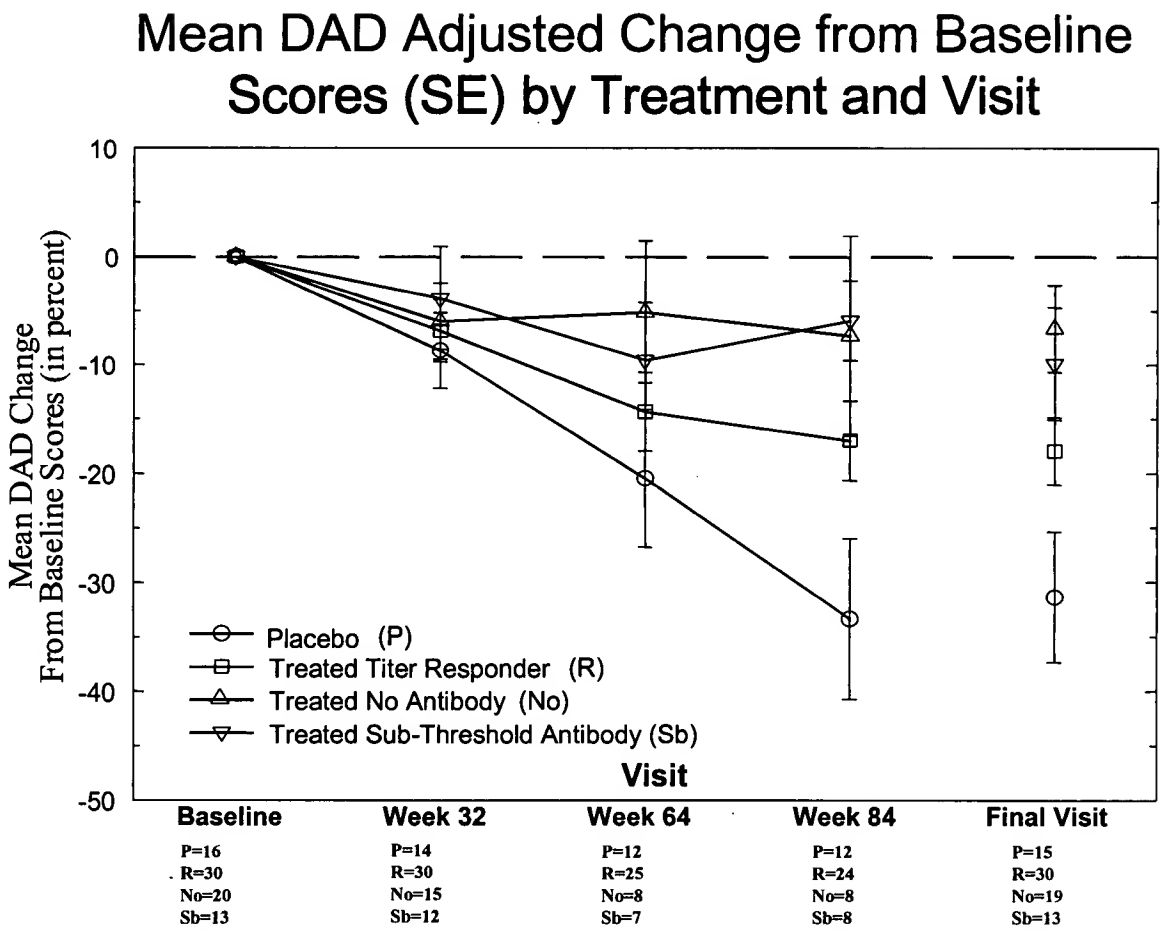
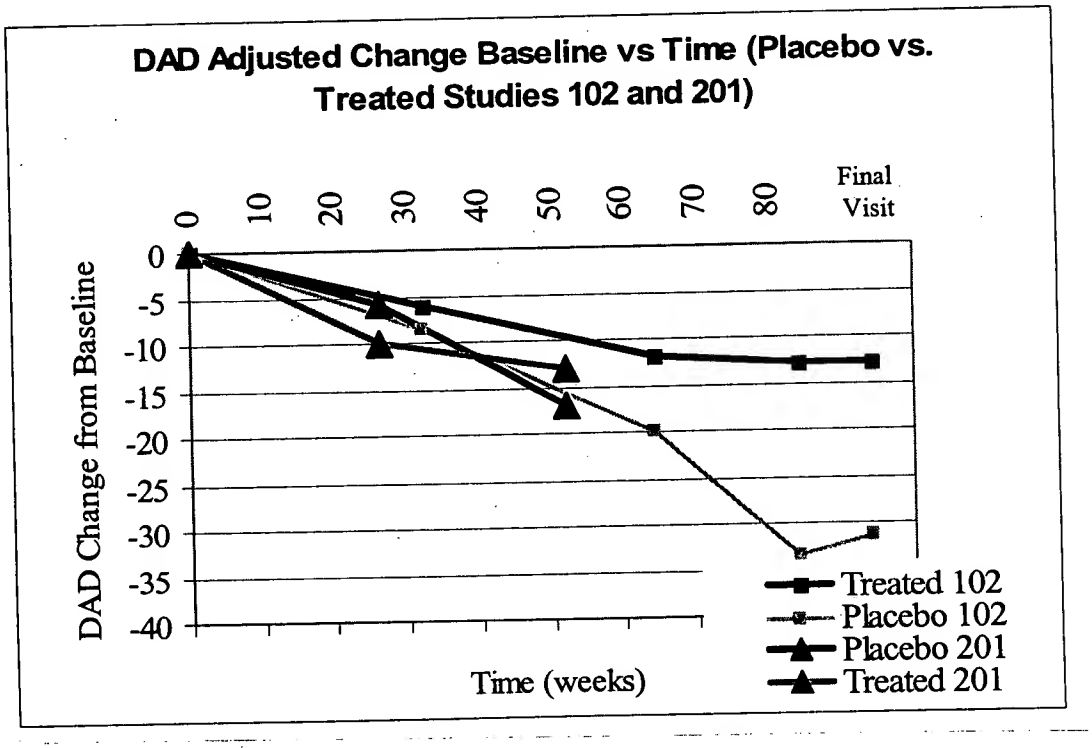


TABLE 1
Total DAD Scores
AN1792 - Protocol 102

FOR slot OTHERS	THERAPY GROUP	NUMBER OF PATIENTS	RAW MEAN SCORE	RAW CHANGE FROM BASELINE	ADJ CHANGE FROM BASELINE	STANDARD ERROR	ADJ MEANS (95% CI.)	DIFF ADJ MEANS (95% CI.) PLACEBO VS OTHERS	P-VALUE PLACEBO VS
BASELINE	1	16	76.56				67.72		
BASELINE	2	30	69.04				67.72		
BASELINE	3	20	64.15				67.72		
BASELINE	4	13	59.27				67.72		
WEEK 32	1	14	68.95	8.69	9.36	3.51	58.67 (50.18,67.16)		
WEEK 32	2	30	62.17	6.86	6.93	2.89	61.10 (55.50,66.71)	2.43 (-7.68,12.55)	0.632
WEEK 32	3	15	58.74	5.99	5.11	3.53	62.92 (54.75,71.09)	4.25 (-7.63,16.14)	0.477
WEEK 32	4	12	54.58	3.86	3.37	4.79	64.67 (55.50,73.83)	6.00 (-6.68,18.68)	0.348
WEEK 64	1	12	60.18	20.48	22.54	6.30	49.38 (38.23,60.53)		
WEEK 64	2	25	57.98	14.35	14.82	3.63	57.09 (49.57,64.62)	7.72 (-5.66,21.10)	0.251
WEEK 64	3	8	57.86	5.12	6.74	6.58	65.17 (51.15,79.19)	15.79 (-2.32,33.91)	0.086
WEEK 64	4	7	56.07	9.60	9.23	5.38	62.69 (48.10,77.28)	13.31 (-5.30,31.92)	0.157
WEEK 84	1	12	45.77	33.36	37.17	7.37	34.59 (22.76,46.42)		
WEEK 84	2	24	56.99	17.00	19.30	3.65	52.46 (44.14,60.78)	17.87 (3.75,32.00)	0.014
WEEK 84	3	8	55.63	7.35	8.28	9.23	63.49 (48.71,78.26)	28.90 (9.88,47.91)	0.004
WEEK 84	4	8	56.91	5.91	3.92	3.71	67.84 (53.38,82.31)	33.25 (14.16,52.35)	0.001
VISIT-FINAL	1	15	45.28	31.38	34.44	6.01	33.61 (23.90,43.31)		
VISIT-FINAL	2	30	51.07	17.97	18.48	3.07	49.56 (42.89,56.23)	15.95 (4.25,27.66)	0.008
VISIT-FINAL	3	19	59.02	6.66	6.19	4.03	61.85 (53.17,70.54)	28.25 (15.19,41.30)	0.000
VISIT-FINAL	4	13	49.38	9.89	7.86	5.21	60.18 (49.73,70.64)	26.58 (12.05,41.10)	0.001

Note: Therapy group decode: 1=Placebo; 2=Treated titer Responders; 3=Treated No Antibody; 4=Treated Sub-Threshold Antibody

Figure No. 2


DAD Adjusted Change Baseline vs Time (Placebo vs. Treated Studies 102 and 201)
DAD Change from Baseline
0
-5
-10
-15
-20
-25
-30
-35
-40
0
10
20
30
40
50
60
70
80
Final Visit
Time (weeks)
Treated 102
Placebo 102
Placebo 201
Treated 201

CURRICULUM VITAE

Martin Koller, MD, MPH

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EDUCATION:

B. A.	1968 - 1972	Franklin and Marshall College Lancaster, Pennsylvania
M.P.H. - Epidemiology	1972 - 1973	University of Texas School of Public Health Houston, TX
M.D.	1973 - 1977	University of Maryland School of Medicine Baltimore, Maryland
Post-graduate medical: Internship	1977 - 1978	Mount Zion Hospital San Francisco, California
Residency: Psychiatry	1978 - 1979	Mount Zion Hospital San Francisco, California
Residency: Neurology	1980 - 1983	Kaiser Permanente Hospital University of Southern California and Children's Hospital of Los Angeles, Los Angeles, California
Fellowship: Neuromuscular	1983 - 1984	University of Southern California Director: W. King Engel Good Samaritan Hospital Neuromuscular Center

PROFESSIONAL HISTORY:

Elan Pharmaceutical, Inc.	2/03 - present	Vice President - North America
(Athena Neurosciences, Inc.)	6/99 – 1/03	Senior Director, Clinical Research
San Diego, CA	2/94 – 5/99	Director, Clinical Research
Syntex Pharmaceuticals Institute of Cardiovascular & Central Nervous System Palo Alto, CA	11/90 - 2/94	Associate Medical Director

Wyeth-Ayerst Laboratories Clinical Research, CNS Group Radnor, PA	6/90 - 11/90	Associate Medical Director
Northridge Neurological Group Northridge, California	8/84 - 5/90	Neurologist

MEDICAL LICENSES: California: A-32848
Pennsylvania: MD-042008-L

BOARD CERTIFICATION: Diplomate - Specialty of Neurology
American Academy of Psychiatry and Neurology - #29297, 1987

ACADEMIC APPOINTMENTS: Clinical Instructor of Neurology
Department of Neurology
University of Southern California, 1983-1984

PHARMACEUTICAL INDUSTRY EXPERIENCE:

As Vice President of Clinical Development for North America at Elan:

- Leadership and management of a group of approximately 70 clinical development employees (MDs, PhDs, monitors and other administrative staff)
- Responsible for defining and representing clinical strategic and development issues for the Elan organization
- Member of several Elan strategic management committees and teams to set, integrate and achieve overall corporate goals and objectives
- Lead of protocol review initiative to ensure consistent, quality scientific input and review of all Phase I-III projects
- Liaison between European and American clinical development structures to ensure consistent quality for all programs and submissions worldwide
- Integration of new clinical development Standard Operating Procedure processes within the North America Group

Projects and Submissions:

- Multiple IND's filed, 2 NDA's, 1 BLA; multiple phase I-III studies
- Immunotherapeutic Programs for the indication of Alzheimer's disease (4 distinct programs in Alzheimer's disease): AN1792, AAB, ACC, ELN90543
- Beta-secretase program in Alzheimer's disease
- Antegren (monoclonal antibody) for the indication of multiple sclerosis
- Botulinum Toxin Type B (MYOBLOC™, NeuroBloc®) for the indication of cervical dystonia (BLA clinical lead, PI Clinical Negotiation Team Representative, approved 12/00)
- Ciliary Neurotrophic Factor (rhCNTF) for the indication of amyotrophic lateral sclerosis
- DiaStat® for the indication of epilepsy (NDA submission clinical review team)
- Lifarizine for the indication of stroke

Nerve Growth Factor (NGF) for the indication of Alzheimer's disease

Zanaflex® for the indication of spasticity (NDA submission clinical review team)

CDER and CBER experience with 3 applications submitted to FDA (2-NDAs and 1-BLA), multiple IND submissions and regulatory interactions

CLINICAL RESEARCH EXPERIENCE PRIOR TO INDUSTRY:

Immunosuppressive regimens for the treatment of dysimmune dysschwannian neuropathies and inflammatory myopathies

Etiocholanolone and Poly-ICLC for the treatment of dysimmune dysschwannian neuropathies

TRH for the treatment of amyotrophic lateral sclerosis

Dietary manipulations for the treatment of carnitine palmityl transferase deficiency

MANAGEMENT:

Manage a clinical department group (approximately 70 employees) reporting to the President of R&D for several programs (e.g., Alzheimer's disease, multiple sclerosis, epilepsy, pain, Parkinson's disease)

Managed several clinical development programs with multiple staff members and CRO's

Study leader/clinical leader for several projects (national and international project teams)

Consultant and Medical Expert for several CNS project on multiple Joint Venture Teams

Attended several Management Courses (Project Team Leadership, Total Quality Management, Management Training Seminars, Interview and Selection Skills Workshop, Statistical Concepts for Non-Statisticians, etc.)

PAPERS/ABSTRACTS/PUBLICATIONS:

PAPERS:

Cullis P, Moore P, Freeman A, Kumar R, Hammerstad J, Tarsy D, Duane D, Fross R, Massey J, Reich S, Sethi K, Walker F, Hyman N, Swenson M, Lees A, Barnes M, Murray J, Donoghue S, Groves L, Wilmer-Hulme A, Wallace J, and **Koller M**. An Open-Label, Forced Dose-Escalation Safety Study Of Myobloc™ (Botulinum Toxin Type B) In Patients With Cervical Dystonia. *In preparation.*

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Updated: Feb 2003